REMARKS

Claims 1-88 have been canceled.

Claims 89-120 are pending, are drawn to the elected species of invention, and are currently under prosecution. Applicants acknowledge that the Examiner is likely to withdraw method claims 101-120 as being drawn to a non-elected invention or species of invention.

Claims 89 and 90 are amended.

Support for amendments to the claims and new claims

Specific support for the combination of CDRs recited in the elected species can be found, for example, at lines 4-9 of page 35 of the specification.

Support for the amendments to claims 89 and 89 can be found throughout the specification as filed, such as, for example, at lines 16-32 of page 21 and lines 103 of page 22 of the specification as well as the original claims, examples and figures.

Support for new claim 91 can be found, for example, in previous claim 44 and the specification as filed.

Support for new claims 92 and 94 can be found, for example, in previous claims 2, 21 and 22 and the specification as filed.

Support for new claim 93 can be found, for example, in previous claims 44-61 and the specification as filed.

Support for new claim 95 can be found, for example, in previous claim 42 and the specification as filed.

Support for new claim 96 can be found, for example, in previous claim 43 and the specification as filed.

Support for new claims 97 and 99 can be found, for example, in previous claim 46 and the specification as filed.

Support for new claims 98 and 100 can be found, for example, in previous claim 47 and the specification as filed.

Support for new claims 101-103 can be found, for example, in previous claims 44-47 and the specification as filed.

Support for new claims 105-107 can be found, for example, in previous claims 48-50 and the specification as filed.

Support for new claims 108-111 can be found, for example, in previous claims 51-54 and the specification as filed.

Support for new claims 112-114 can be found, for example, in previous claims 55-57 and the specification as filed.

Support for new claims 115-117 can be found, for example, in previous claims 58-60 and the specification as filed.

Support for new claims 118-120 can be found, for example, in previous claims 61-63 and the specification as filed.

Scope of the claims

Applicants maintain for the reasons of record that the claims in previously filed responses fully meet the requirements of 35 U.S.C § 112, first paragraph. However, solely in an effort to further prosecution, Applicants have amended the claims to recite embodiments related to the elected species and will file a continuing application to address broader issues. Arguments presented herein address the elected species recited in the amended claims provided herein. Applicants reserve the right to prosecute any canceled subject matter in a continuing application.

Currently recited composition claim 90 encompasses an antibody, or functional fragment thereof, wherein said antibody, or functional fragment thereof, comprises: a heavy chain CDR1 referenced as SEQ ID NO:45 or SEQ ID NO:45 having a conservative substitution therein; a heavy chain CDR2 referenced as SEQ ID NO:155 or SEQ ID NO:155 having a conservative substitution therein; a heavy chain CDR3 referenced as SEQ ID NO:63 or SEQ ID NO:63 having a conservative substitution therein; a light chain CDR1 referenced as SEQ ID NO:157 or SEQ ID NO:157 having a conservative substitution therein; a light chain CDR2 referenced as SEQ ID NO:22 or SEQ ID NO:22 having a conservative substitution therein; and a light chain CDR3 referenced as SEQ ID NO:77 or SEQ ID NO:77 having a conservative substitution therein.

Currently recited composition claim 89 encompasses a grafted antibody, or functional fragment thereof, wherein said grafted antibody, or functional fragment thereof, comprises: a heavy chain CDR1 referenced as SEQ ID NO:45 or SEQ ID NO:45 having a conservative substitution therein; a heavy chain CDR2 referenced as SEQ ID NO:155 or SEQ ID NO:155 having a conservative substitution therein; a heavy chain CDR3 referenced as SEQ ID NO:63 or SEQ ID NO:63 having a conservative substitution therein; a light chain CDR1 referenced as SEQ ID NO:157 SEQ ID NO:157 having a conservative substitution therein; a light chain CDR2 referenced as SEQ ID NO:22 or SEQ ID NO:22 having a conservative substitution therein; and a light chain CDR3 referenced as SEQ ID NO:77 or SEQ ID NO:77 having a conservative substitution therein, wherein the heavy chain CDRs are grafted into a VHIII/JH6 heavy chain variable region framework referenced as SEQ ID NO:8

Rejoinder

Currently recited claims 101-120 encompass methods of using the antibodies of claims 89 and 90. The method claims have been amended to recite the composition claims currently under consideration. Applicants respectfully request that the method claims be rejoined upon allowance of the composition claims in accordance with *In re Ochiai* and *In re Brouwer*.

35 U.S.C. § 112, 1, scope of enablement

Applicants maintain for the reasons of record that the claims in previously filed responses fully meet the requirements of 35 U.S.C § 112, first paragraph, scope of enablement. However, solely in an effort to further prosecution, Applicants have amended the claims to recite embodiments related to the elected species and will file a continuing application to address broader issues. Arguments presented herein address the elected species recited in the amended claims provided herein. Applicants reserve the right to prosecute any canceled subject matter in a continuing application.

Applicants submit that one of skill in the art would recognize that given the general teachings of the specification as filed with respect to the CDRs, modifications to said CDRs (conservative and non-conservative) and the presence of working examples, the specification as filed provides a

broader blueprint for the claimed embodiments than acknowledged by the Examiner to date. The specification teaches how to make and use the claimed antibodies and functional fragments thereof for greater than the full breadth of the claims and provides more than sufficient support to show how to make and use the claimed elements in accordance with the Wands factors. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants respectfully assert that the following teachings of the specification broadly show how to make and use the embodiments for the full scope of the currently recited claims (as well as a broader scope) and provide basis for enablement of not only the currently recited claims, but a much broader genus of antibodies.

1. Skill of the art and the quantity of experimentation

A patent need not teach, and preferably omits, what is well-known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

The level of skill in the art of making and using antibodies is high. The level of skill in the art of making and using modified polypeptides (e.g., antibodies) is high. The level of skill in the art of making and using grafted and humanizing antibodies is high. The level of skill in the art of testing the function of such modified antibodies is high.

The Federal Circuit has made clear that making and using antibodies does not involve undue experimentation. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81 94 (Fed. Cir. 1986). Further, it is also well-settled in the law that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982).

Even in the relatively "unpredictable" arts, one need not necessarily disclose how to make each and every embodiment encompassed by the claim. For example, in *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976), the court noted that some experimentation is often to be expected in unpredictable areas of technologies. The court further observed that if § 112 required a disclosure of a test with every species covered by a claim in an unpredictable art, then a prohibited number of actual experiments would have to be performed, discouraging the filing of patent applications in unpredictable areas. *Id.*

It is a discovery of the inventors that antagonists that specifically bind to a denatured collagen with higher affinity than to the native collagen block angiogenesis. Such specificity to a denatured collagen is a sufficient selective criteria that can be used to identify and isolate any type of antagonist claimed in the present invention, including antibodies and synthetic peptides. Thus, the present invention teaches a general method for identification of antagonists based on their higher binding affinity to denatured collagens as compared to the native collagens.

Applicants assert that any experimentation needed to practice the invention as described and claimed is routine. The skilled artisan that conducts experiments to produce a single monoclonal antibody of interest routinely makes and tests hundreds, if not thousands, of antibodies. Methods of testing the function modified antibodies using common and art-recognized assays, such as an ELISA or FACS analysis, have been routine for well over 20 years. Such methods of testing are provided in the specification as filed. Thus, based on the broad disclosure of the specification, any experimentation is routine with respect to the recited compositions currently claimed.

2. *Elected species and broader teachings of HUIV26 antibodies (breadth of the claims, the nature of the invention, and the existence of working examples)*

The Examiner states at page 6 of the Office Action that the specification does not reasonably provide enablement for making and using an antibody or a functional fragment thereof that has at least a two-fold higher binding activity for denatured collagen over native collagen, wherein said antibody or functional fragment comprises the three heavy chain CDRs of SEQ ID NOS: 45, 155 and 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NOS 157, 22 and 77, or any other variant of monoclonal antibody HUIV26, which is encompassed by the generic claims.

Applicants respectfully disagree and direct the Examiner's attention to the following teachings of the specification.

(a) Specific support for the combination of CDRs recited in the elected species can be found, for example, at lines 4-9 of page 35 of the specification. Applicants note that, at this section of the specification, the combination of CDRs is designated DcomD7.

(b) Figure 6 and the description thereof provide the modifications of the CDRs compared to wild-type. DcomD7, DhuG5 and DhuH8 are grouped together in the table.

(c) DhuG5 is demonstrated as preferentially binding to denatured collagen IV over native collagen in Figure 8, demonstrating a working example of an antibody having specificity for a cryptic epitope on denatured collagen.

(d) Figure 10 shows the binding activity of the HUIV26 variant DhuH8 antibody and functional fragments thereof (Fab and IgG forms) to denatured collagen, but not native collagen. Thus, it is very clear that both the Fab and IgG forms of DhuH8 bind with "at least two-fold higher binding activity for denatured collagen over native collagen" in direct contrast with the Examiner's statements.

Applicant has provided working examples meeting the scope of the claims. MPEP § 2164.02 makes clear that applicant need not describe ever last detail of an invention to fulfill the enablement requirement. Applicant is not required to set forth each and every detail of the claimed invention to illustrate how to make and use the claimed invention. *In re Gay*, 309 F.2d 769, 774, 135 USPQ 311, 316 (CCPA 1962).

Further, MPEP § 2164.03 sets forth the premise that for a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. The level of skill, the state of the art and the teachings in the specification have been discussed in greater detail in this response.

Other relevant teachings of the specification with respect to HUIV26 variants

In a broader application supporting the previously filed claims, the specification teaches mutations in combinatorial variants of the HUIV26 antibody at lines 16-22 of page 5 with respect to Figure 6. Figure 6 shows specific examples of twenty-four (24) representative examples of beneficial mutations for HUIV26 variants. Mutations include both conservative and non-conservative mutations.

The specification also teaches a multitude of combinations of heavy and light chain CDRs of modified HUIV26 antibodies at pages 32-35 of the specification.

Figure 8 illustrates that the modified antibodies, and functional fragments thereof, preferably bind to denatured collage compared to native collagen.

Figure 10 illustrates that the modified antibodies, and functional fragments thereof, have at least a two-fold higher binding activity for denatured collagen over native collagen.

3. Conservative and non-conservative modifications

Support for the recited elements of "SEQ ID NO: X or SEQ ID NO: X having a conservative substitution therein" in the claims can be found throughout the specification as filed such as, for example, at lines 16-32 of page 21 and lines 103 of page 22 of the specification as well as the original claims, examples and figures.

The specification teaches at line 31 of page 21 through line 3 of page 22 that other minor modifications (e.g., non-conservative modifications) can be made so long as the polypeptide retains some or all of its function, i.e., binding to cryptic epitopes on denatured collagen.

Thus, the specification teaches that mutations, including both conservative and non-conservative mutations, can be made to HUIV26 antibodies as long as the antibody or functional fragment thereof retains some or all of their function.

The specification teaches HUIV26 antibodies, variants thereof and functional fragments thereof at line 3 of page 28 through line 27 of page 25.

The specification teaches beneficial CDR mutations for anti-cryptic collagen site antibodies at lines 26-31 of page 4 and lines 1-5 of page 5 with respect to Figure 4.

Figure 6 and the description thereof provide the modifications of the CDRs compared to wild-type. Modifications are both conservative and non-conservative and include those in CDRs and in "framework" regions.

Thus, Applicants assert that the specification as filed provides basis for both conservative and non-conservative modifications and specific examples of each. Applicant is not required to provide working examples of each and every possible variation of the claimed elements. *In re Gay*, MPEP § 2164.03, *Id.* In view of the disclosure of the specification, Applicants have provided a broad blueprint for making a using an entire genus of antibodies and functional fragments thereof as claimed in previous responses and the present response.

4. Binding and activity

Testing the functionality of antibodies, functional fragments thereof, and modifications of both, is set forth in the specification such as, for example, at lines 12-19 of page 65 which teach methods for measuring binding affinity of the modified antibodies.

The specification teaches the activity and specificity of HUIV26 variants at lines 1-6 of page 6 with respect to Figure 8.

The specification shows the binding activity of the HUIV26 variant DhuH8 (Fab and Ig forms) to native and denatured collagen at lines 13-16 of page 6 with respect to Figure 10.

Example IV of the specification teaches binding activity and specificity of HUIV26 antibodies and variants thereof at line 5 of page 89 through line 11 of page 91.

The specific CDRs recited throughout the specification as filed clearly illustrate that Applicants have provided a broad teaching showing that not only can conservative mutations be made, but also non-conservative mutations can be made, and both types of modifications result in functional antibodies and fragments thereof. In addition to providing support for the elected species, which is a modified form of HUIV26, the specification provides seventeen (17) other representative exemplary combinations of CDRs comprising HUIV26 variants at line 12 of page 32 through line 27 of page 35.

5. Request for withdrawal of rejection under 35 U.S.C. § 112 1st paragraph, scope of enablement

Considering that the skill in the art of making and using antibodies, modifying polypeptides (e.g., antibodies) and humanizing antibodies is high, one skilled in the art would recognize that given the general teachings with respect to the combinations of CDRs, modifications to said CDRs (conservative and non-conservative) and the provision of over 24 representative examples, the specification provides a broader blueprint for the claimed embodiments than acknowledged by the Examiner to date. Thus, the specification teaches how to make and use the claimed antibodies and functional fragments thereof for greater than the full breadth of the claims and provides more than sufficient support to show that Applicants have fully disclosed how to make and use the claimed elements.

Based on the broad teachings of the specification, Applicants believe that the rejection based on lack of enablement for the full scope of the claims has been overcome and respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 112 §, first paragraph.

35 U.S.C. § 112, 1 – Written Description

Applicants maintain for the reasons of record that the claims in previously filed responses fully meet the requirements of 35 U.S.C § 112, first paragraph, written description. However, solely in an effort to further prosecution, Applicants have amended the claims to recite embodiments related to the elected species and will file a continuing application to address broader issues. Arguments presented herein address the elected species recited in the amended claims provided herein. Applicants reserve the right to prosecute any canceled subject matter in a continuing application.

The written description requirement can be met by disclosure of a "sufficiently known" structure in correlation with a functional characteristic, as described in *Enzo Biochem v. Gen-Probe, Inc.*:

> In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics."

(Quoting from *Guidelines*, 66 Fed. Reg. at 1106) (*Enzo Biochem v. Gen-Probe, Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002).

In fact, the functional characteristic disclosed in the claims of the *Enzo* patent was preferential binding for one substrate over another:

> "under the [USPTO Application of Written Description] Guidelines, the written description requirement would be met for all of the claims of the '659 patent if the functional characteristic of preferential binding to N. gonorrhoeae over N. meningitidis were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement."

(*Id.*) The present application claims antibodies based on a combination of both functional and structural characteristics. The disclosed correlation, of the higher relative binding activity for denatured than native collagen with the specified CDR amino acid sequences, provides more than sufficient written description for the claims under 35 U.S.C. § 112 ¶ 1.

The Examiner argued at page 19 of the Office action that the written description rejection was supported by the *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886, 1984 (CAFC 2004) decision. Applicants respectfully note that the present application could not differ more drastically than the decision cited in *University of Rochester v. G.D. Searle Co., Id.* In *University of Rochester v. G.D. Searle Co.*, the specification did not provide even *one* example meeting the elements of the claims. In the present case, Applicants have provided over 24 representative examples and have provided the examples and Figures as support to show that they are working embodiments. Thus, the *University of Rochester v. G.D. Searle Co.* decision is not applicable to the present case.

As argued of record, the Federal Circuit has made clear that the structure of claimed antibodies does not have to be stated at all. *Noelle v. Lederman*, 355 F.3d 1343, 69 USPQ2d 1508 (Fed. Cir. 2004). In *Noelle v. Lederman et al.*, (Fed. Cir., 2004) No. 02-1187, the Federal Circuit has summarized the written description requirements with respect to antibodies as follows: "as long as an applicant has disclosed a 'fully characterized antigen,' either by its **structure, formula, chemical name, or physical properties**, or by depositing the protein in a public depository, the

applicant can then **claim an antibody by its binding affinity** to that described antigen (*Id.* at page 12, emphasis added).

In the present application, monoclonal antibodies HUI77 and HUIV26 are claimed by their binding specificity to a particular antigen, a denatured collagen type-I (HUI77) or denatured collagen type-IV (HUIV26). Since the antigens are characterized by their chemical name (denatured collagen type I and denatured collagen type IV), according to the *Noelle* decision, applicants properly claimed the antibodies. According to the Court, "[i]f Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the 'fully characterized' antigen." (*Id.*, at 1349) This case thus builds on the Court's findings in Enzo.

MPEP § 2163.02 and the written description guidelines set forth the standard for determining compliance with the written description requirement.

1. "An objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'" *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).
2. The "fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USOQ2d 1111, 1117 (Fed. Cir. 1991).
3. Applicant can show possession using descriptive words, structures, figures, diagrams and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).
4. Possession can be shown by actual reduction to practice, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1988).

In the present case, as discussed *supra*, the specification as filed provides over 24 representative species of modified HUIV26 antibodies wherein modifications are made to heavy chain CDRs having polypeptide sequences as set forth in SEQ ID NOS: 26, 28 and 30 and light

chain CDRs polypeptide sequences as set forth in SEQ ID NOS: 20, 22 and 24, one of which is the elected species. Thus, the specification provides working examples illustrating that such modified HUIV26 antibodies, and functional fragments thereof, are capable of binding to denatured collagen (*see* Figure 8 and the description thereof) and that the antibodies, and functional fragments thereof have at least a two-fold higher binding activity for denatured collagen over native collagen (*see* Figure 10 and the description thereof). Thus, Applicants have reduced the recited embodiments to practice, have described distinguishing identifying characteristics of the claimed antibodies and functional fragments thereof, and have provided descriptive words, structures, figures, diagrams and formulas that fully set forth the claimed invention, and indeed a broader scope of invention. Thus, the description as filed clearly allows persons of ordinary skill in the art to recognize that Applicants invented and have possession of what is claimed.

For the reasons set forth above, Applicants respectfully request that the rejections of claims under 35 U.S.C. § 112, ¶ 1 for lack of written description be withdrawn.

35 U.S.C. § 112, 1st paragraph, new matter

The Federal Circuit has made clear that there can be adequate written description for applicant's claim limitation even though is was not set forth "in *haec verba*" in the specification. *In re Wright*, 866 F.2d at 422, 9 USPQ2d at 1649 (Fed. Cir. 1989).

In the present case, Applicants have not made amendments to the specification and support for the claims can be found throughout the specification as filed as discussed *supra*. MPEP § 2163.06 does not require that Applicants provide literal, verbatim support for each and every claim limitation to show that the specification provides support for the claim limitation. Applicants maintain that the claims are fully supported by the general teachings of the specification and the specific examples of conservative and non-conservative modifications to the CDRs as discussed *supra*.

Thus, Applicants respectfully submit that the application as filed provides full support for the presently recited claims, that no new matter has been added and request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants believe that for the reasons set forth above, the Examiner's rejection of the claims have been overcome. Thus, Applicants respectfully request that the Examiner allow the composition claims and rejoin the method claims.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (referencing 30797-711.201).

The Examiner is invited to call the undersigned agent at 858.350.2382 with any questions.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
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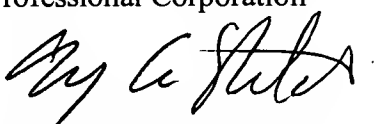

Dated March 30, 2006

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